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<p>(21) International Application Number: PCT/SE92/00055</p> <p>(22) International Filing Date: 29 January 1992 (29.01.92)</p> <p>(30) Priority data: 9100341-8 4 February 1991 (04.02.91) SE</p> <p>(71) Applicant (for all designated States except US): AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): ANDERSSON, Paul [SE/SE]; Gullvingevägen 12, S-240 17 Södra Sandby (SE). AXELSSON, Bengt [SE/SE]; Lillegårdsvägen 5, S-240 13 Genarp (SE). BRATTSAND, Ralph [SE/SE]; Skolmästarvägen 4, S-223 67 Lund (SE). THALEN, Arne [SE/SE]; Morkullevägen 35, S-237 00 Bjärred (SE).</p>		<p>(74) Agents: DANIELSSON, Sten et al.; AB Astra, Patent Department, S-151 85 Södertälje (SE).</p> <p>(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published With international search report.</p>
<p>(54) Title: NOVEL STEROIDS</p> <div style="text-align: center; margin: 20px 0;"> <p>(I)</p> </div> <p>(57) Abstract</p> <p>Compounds of general formula (I) in the form of a 22R and 22S epimer, wherein X₁ and X₂ are the same or different and each represents a hydrogen atom or a fluorine atom, provided that X₁ and X₂ are not simultaneously a hydrogen atom, processes for their preparation, pharmaceutical preparations containing them and the use of the compounds in the treatment of inflammatory and allergic conditions.</p>		

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Novel steroids5 Field of invention

The present invention relates to novel anti-inflammatory and anti-allergic active compounds and to processes for their preparation. The invention also relates to pharmaceutical compositions containing the compounds and
10 to methods of the pharmacological use of the compounds.

The object of the invention is to provide an anti-inflammatory, immunosuppressive and anti-allergic glucocorticosteroid or a pharmaceutical composition
15 thereof with high activity at the application place, e.g. in the respiratory tract, on the skin, in the intestinal tract, in the joints or in the eye directing the drug to a delimited target area, thereby inducing low glucocorticoid systemic effects.

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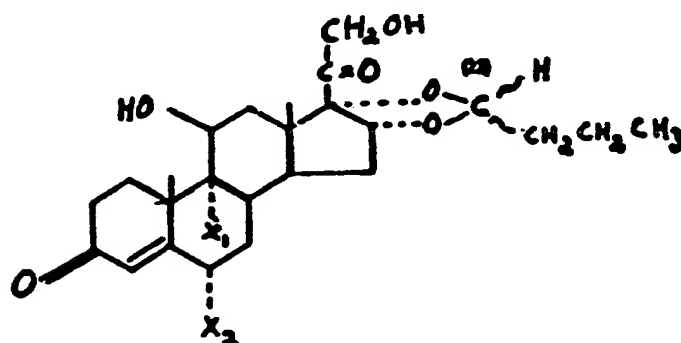
Background art

It is known that glucocorticosteroids (GCS) can be used for local therapy of inflammatory, allergic or immunologic diseases in respiratory airways (e.g. asthma, rhinitis), in skin (eczema, psoriasis) or in bowel
25 (ulcerative colitis, Morbus Crohn). With local glucocorticosteroid therapy, clinical advantages over general therapy (with e.g. glucocorticosteroid tablets) are obtained, especially regarding reduction of the
30 unwanted glucocorticoid effects outside the diseased area due to reduction of the necessary dose. To reach even higher clinical advantages, in e.g. severe respiratory airway disease, GCS must have a suitable pharmacological profile. They should have high intrinsic glucocorticoid
35 activity at the application site but also a rapid inactivation before or after uptake into the general circulation.

Disclosure of the invention

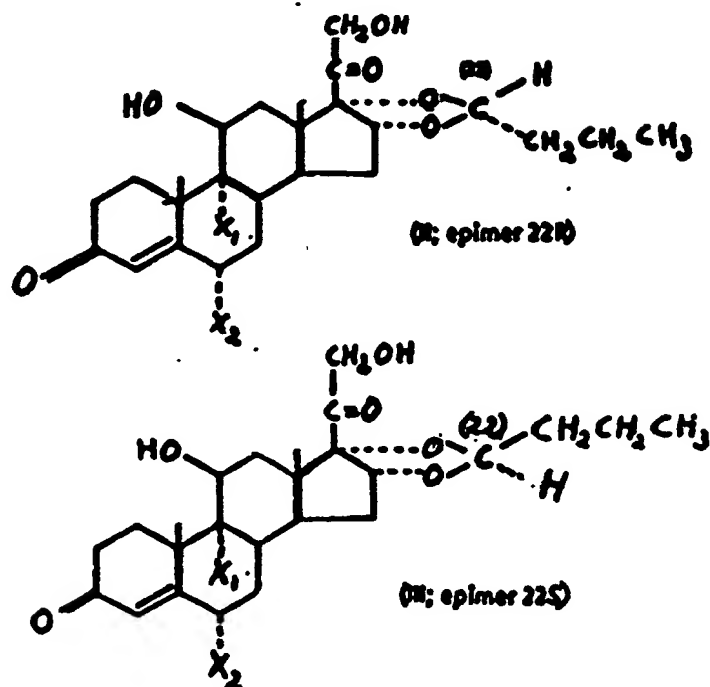
One object of the invention is to describe new GCS compounds. They are characterized by high anti-inflammatory, immunosuppressive and anti-anaphylactic potency at the application site and particularly they have a markedly improved relationship between that potency and the activity to provoke GCS actions outside the treated region.

The compounds of the invention are a 22R or 22S epimer of a compound of the general formula



wherein X₁ and X₂ are the same or different and each represents a hydrogen atom or a fluorine atom, provided that X₁ and X₂ are not simultaneously a hydrogen atom.

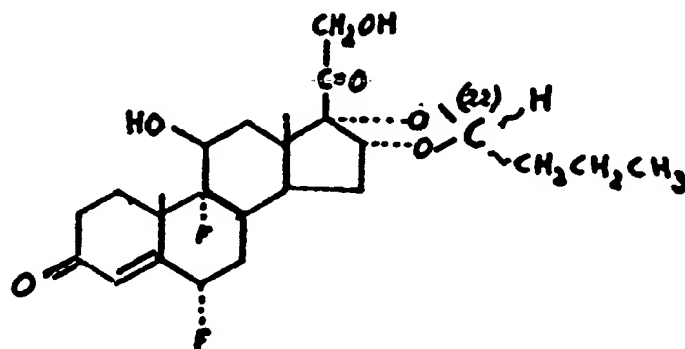
The individual 22R and 22S epimers of the formula (I) can be elucidated in the following way due to the chirality at the carbon atom in 22-position:



wherein X₁ and X₂ are as defined above.

An epimer 22R and 22S, respectively, of formula I above is by definition a compound containing not more than 2 per cent by weight, preferably not more than 1 per cent by weight of the other epimer.

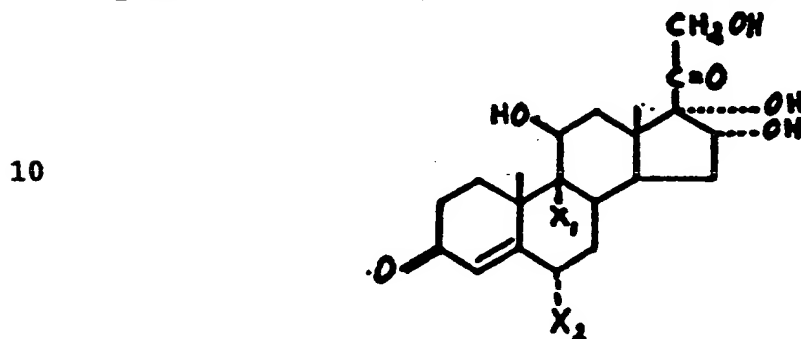
The preferred compounds of the invention are the 22R and 22S epimers of the structure



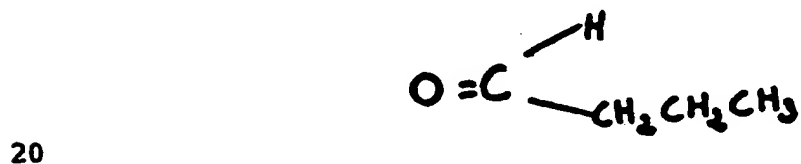
The preferred steroid has the R configuration at the 22 carbon atom.

Methods of preparation

- 5 The 16 α ,17 α -acetals of the formula I are prepared by reaction of a compound with the formula

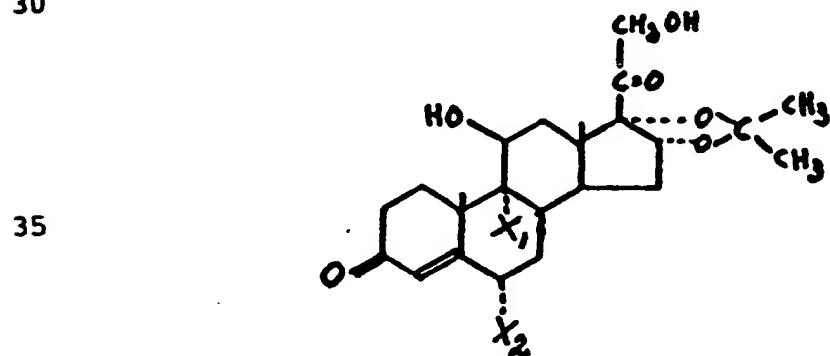


- 15 wherein X₁ and X₂ have the above given definition, with an aldehyde of the formula

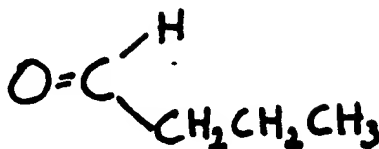


- The reaction is carried out by adding the steroid to a solution of the aldehyde together with an acid catalyst, e.g. perchloric acid, p-toluenesulfonic acid, hydrochloric acid in an ether, preferably dioxane or in
25 acetonitril.

- The compounds of the formula I, are also prepared by transacetalisation of the corresponding 16 α , 17 α -acetonides
30



wherein X_1 and X_2 have the above given definition,
with an aldehyde of the formula



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The reaction is carried out by adding the steroid to a solution of the aldehyde together with an acid catalyst, e.g. perchloric acid, p-toluenesulfonic acid,
10 hydrochloric acid in an ether, preferably dioxane, or in acetonitril.

The reaction can also be performed in a reaction medium which is a hydrocarbon, preferably isooctane, wherein the
15 solubility of the pregnane derivative (the 16,17-acetonide or the 16,17-diol) is less than 1 mg/l, or in a halogenated hydrocarbon, preferably methylene chloride or chloroform.

20 The reaction is catalysed by a hydrohalogen acid or an organic sulphonic acid such as p-toluenesulfonic acid.

The reaction is performed in the presence of small grains of an inert material, such as glass, ceramic, sifted
25 silicone dioxide (sand) or inert metal particles, such as granulated stainless steel or tantalum in the reaction medium (when the reaction is performed in a hydrocarbon solvent).

30 The 22R-epimer is so exclusively obtained that it can be sufficiently purified to be used as a pharmaceutical substance by recrystallization instead of by the more expensive chromatographic procedure.

35 At the reaction procedure in hydrocarbons the steroid-catalyst complex will form a big sticky lump which makes stirring and effective reaction impossible.

To overcome this small grains of an inert material and effective stirring is used to prevent the formation of a big lump and instead divide the steroid-catalyst complex into a thin layer around the grains. Thereby, the reactive surface will be much larger and the reaction with the carbonyl compound proceeds very rapidly.

The inert grain material used in the process, preferably silicone dioxide (SiO_2), should consist of free-flowing small particles. The particles size is ranging from 0,1-1,0 mm, preferably 0,1-0,3 mm. The amount used in the reaction will range from 1:5 to 1:50, preferably 1:20.

With hydrohalogen acid is to be understood hydrofluoric, hydrochloric, hydrobromic and hydroiodic acid and the corresponding oxohalogen acids, such as perchloric acid.

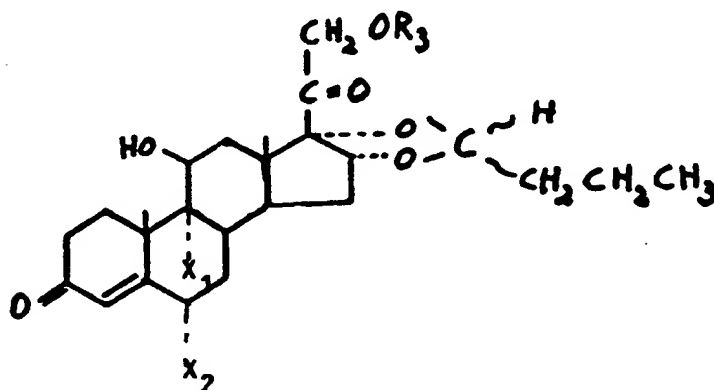
The individual 22R and 22S epimers, which are formed at the acetalisation, possess practically identical solubility characteristics. Accordingly, they have turned out to be impossible to separate and isolate from the epimeric mixture by conventional methods for resolution of stereoisomers, e.g. fractional crystallization. In order to obtain the individual epimers separately, the stereoisomeric mixtures according to the formula I above are subject to column chromatography, thus separating the 22R and 22S epimers in view of different mobility on the stationary phase. The chromatography may be carried out for instance on cross-linked dextran gels of the type Sephadex LH, e.g. Sephadex LH-20 in combination with a suitable organic solvent as eluting agent. Sephadex LH-20, prepared by Pharmacia Fine Chemicals AB, Uppsala, Sweden, is a beadformed hydroxypropylated dextran gel wherein the dextran chains are cross-linked to give a three-dimensional polysaccharide network. As mobile phase, halogenated hydrocarbons, e.g. chloroform or a mixture of

heptane-chloroform-ethanol in the proportions 0-50:50-100:10-1, has successfully been used, preferably a 20:20:1 mixture.

- 5 Alternatively, the chromatography may be carried out on microparticulate bonded phase columns, e.g. 10 μ m octadecylsilane (μ Bondapak C₁₈) or μ Bondapak CN columns in combination with a suitable organic solvent as mobile phase. Ethanol-water mixtures in the proportions 40-60:60-40 have successfully been used.

The epimers 22R and 22S can also be obtained from a stereoisomeric mixture with the general formula

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IV

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- 25 wherein X_1 and X_2 have the above given definition and R_3 is a carboxylic acid rest having a straight hydrocarbon chain having 1-5 carbon atoms preferably the 21-acetate, after resolution by chromatography on Sephadex LH-20 together with a suitable solvent or mixture of solvents, e.g. heptane-chloroform-ethanol in the proportions 0-50:50-10:10-1, preferably 20:20:1, as mobile phase. The separated and isolated epimers 22R and 22S with the general formula (IV) above are submitted to base catalyzed hydrolysis with hydroxides, carbonates or hydrogen carbonates of alkaline metals, e.g. sodium or potassium hydroxide, sodium or potassium carbonate or sodium or potassium hydrogen carbonate to give the epimers 22R and 22S of the formula II and III respectively, above. The hydrolysis can alternatively be performed with an acid

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as catalyst, e.g. hydrochloric acid or sulfuric acid.

The compounds of the formula IV are prepared according to methods described in the companion application no

5 (our case D 1093-1 SE).

Pharmaceutical preparations

The compounds of the invention may be used for different modes of local administration dependent on the site of inflammation, e.g. percutaneously, parenterally or for
10 local administration in the respiratory tract by inhalation. An important aim of the formulation design is to reach optimal bioavailability of the active steroid ingredient. For percutaneous formulations this is
15 advantageously achieved if the steroid is dissolved with a high thermodynamic activity in the vehicle. This is attained by using a suitable system or solvents comprising suitable glycols, such as propylene glycol or 1,3-butandiol either as such or in combination with water.

20 It is also possible to dissolve the steroid either completely or partially in a lipophilic phase with the aid of a surfactant as a solubilizer. The percutaneous compositions can be an ointment, an oil in water cream, a
25 water in oil cream or a lotion. In the emulsion vehicles the system comprising the dissolved active component can make up the disperse phase as well as the continuous one. The steroid can also exist in the above compositions as a micronized, solid substance.

30 Pressurized aerosols for steroids are intended for oral or nasal inhalation. The aerosol system is designed in such a way that each delivered dose contains 10-1000 µg, preferably 20-250 µg of the active steroid. The most
35 active steroids are administered in the lower part of the dose range. The micronized steroid consists of particles substantially smaller than 5 µm, which are suspended in a propellant mixture with the assistance of a dispersant,

salt of dioctylsulphosuccinic acid.

The steroid can also be administered by means of a dry powder inhaler.

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One possibility is to mix the micronized steroid with a carrier substance such as lactose or glucose. The powder mixture is dispensed into hard gelatin capsules, each containing the desired dose of the steroid. The capsule is then placed in a powder inhaler and the dose is inhaled into the patient's airways.

10

Another possibility is to process the micronized powder into spheres which break up during the dosing procedure. This spheronized powder is filled into the drug reservoir in a multidose inhaler, e.g. Turbuhaler. A dosing unit meters the desired dose which is then inhaled by the patient. With this system the steroid without a carrier substance is delivered to the patient.

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The steroid can also be included in formulations intended for treating inflammatory bowel diseases, either by the oral route or rectally. Formulations for the oral route should be constructed so that the steroid is delivered to the inflamed parts of the bowel. This can be accomplished by different combinations of enteric and/or slow or control release principles. For the rectal route an enema type formulation is suitable.

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30 Working examples

The invention will be further illustrated by the following non-limitative examples. In the examples a flow-rate of $2.5 \text{ ml/cm}^2 \cdot \text{h}^{-1}$ is used at the preparative chromatographic runs. Molecular weights are in all examples determined with chemical ionization mass spectrometry (CH_4 as reagent gas) and the melting points on a Leitz Wetzlar hot stage microscope. The HPLC analyses (High Performance Liquid

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microscope. The HPLC analyses (High Performance Liquid Chromatography) have been performed on a μ Bondapak C₁₈ column (300 x 3.9 mm i.d.) with a flow rate of 1.0 ml/min and with thanol/water in-ratios between 40:60 and 60:40 as mobile phase, if not otherwise stated.

Example 1. 6 α ,9 α -Difluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione.

A solution of 6 α , 9 α -difluoro-16 α -hydroxyprednisolone (2.0 g) in 1000 ml of absolute ethanol was added to a solution of tris(triphenylphosphine)rhodium chloride (2.2 g) in 500 ml of toluene and hydrogenated at room temperature and atmospheric pressure for 7 days. The reaction mixture was evaporated to dryness and methylene chloride (50 ml) was added. The solid precipitate was collected and repeatedly washed with small portions of methylene chloride to give 1.8 g of 6 α ,9 α -difluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione. Molecular weight 414 (calc. 414.5).

Example 2. 6 α ,9 α -Difluoro-11 β ,21-dihydroxy-16 α ,17 α -[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione

A suspension of 0.9 g of tris(triphenylphosphine)rhodium chloride in 250 ml of degassed toluene was hydrogenated for 45 min at room temperature and atmospheric pressure. A solution of 1.0 g of fluocinolone 16 α ,17 α -acetonide in 100 ml of absolute ethanol was added and the hydrogenation was continued for another 40 h. The reaction product was evaporated and the residue purified by flash chromatography on silica using acetone-petroleum ether as mobile phase to remove the main part of the catalyst. The eluate was evaporated and the residue further purified by chromatography on a Sephadex LH-20 column (72.5 x 6.3 cm) using chloroform as mobile phase. The fraction 3555-4125 ml was collected and evaporated yielding 0.61 g of 6 α ,9 α -difluoro-11 β ,21-dihydroxy-16 α ,17 α -[(1-methylethylidene)-bis(oxy)]pregn-4-ene-3,20-dione. Melting point 146-151°C. $[\alpha]_D^{25} = +124.5^\circ$ (c=0.220; CH₂Cl₂). Molecular weight 454

(calc. 454.6). Purity: 98.5% (HPLC-analysis).

Example 3. (22RS)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione.

5 To a solution of freshly distilled butanal (0.5 g) and 0.4 ml of perchloric acid (70%) in 100 ml of purified and dried dioxane, 1.8 g of 6 α ,9 α -difluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione was added in small
10 portions with stirring during 30 min. The reaction mixture was stirred at room temperature for another 5 h. Methylene chloride (600 ml) was added and the solution was washed with aqueous potassium carbonate and water, and dried over anhydrous magnesium sulfate. The crude product obtained
15 after evaporation was purified by chromatography on a Sephadex LH-20 column (76 x 6.3 cm) using chloroform as mobile phase. The fraction 3015-3705 ml was collected and evaporated leaving 1.5 g of (22RS)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoropregn-4-ene-3,20-dione.
20 Molecular weight 468 (calc.468.5).

Example 4. (22R)-16 α , 17 α -Butylidenedioxy-6 α , 9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione.

25 6 α , 9 α -Difluoro-11 β ,21-dihydroxy-16 α , 17 α -[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione (100 mg), 0.03 ml of butanal, 2 ml of fine sand (SiO₂) and 4 ml of heptane were mixed at room temperature. Perchloric acid
30 (70%; 0.1 ml) was added under vigorous stirring. The reaction mixture was stirred at room temperature for another 5 h, cooled and filtered. The solid residue was washed with 4 x 15 ml of aqueous potassium carbonate (10%) followed by 4 x 15 ml of water and then stirred 4 times
35 with 25 ml of dichloromethane. The combined extracts were washed with water, dried and evaporated. The residue was dissolved in a small amount of dichloromethane and precipitated with petroleum ether (b.p. 40-60° C) yielding

75 mg of (22R)-16 α , 17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione mixed with 3 % of the (22S)-epimer. The purity determined by HPLC analysis was 98%. Molecular weight 468 (calc. 468.5).

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Example 5. (22R)- and (22S)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione.

(22RS)-16 α ,17 α -Butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione (1.5 g) was resolved into its 22R- and 22S-epimers by chromatography on a Sephadex LH-20 column (76 x 6.3 cm) using a *n*-heptane-chloroform-ethanol (20:20:1) mixture as mobile phase. The fractions 1845-2565 ml (A) and 2745-3600 ml (B) were collected and evaporated. The two products were precipitated from methylene chloride - petroleum ether. The product from fraction A (332 mg) was identified with ¹H-NMR and mass spectrometry to be (22S)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione and the product from the B fraction (918 mg) as the 22R-epimer.

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The epimers had the following properties. Epimer 22S: Melting point 231-44°C; $[\alpha]_D^{25} = +84.4^\circ$ (c=0.096; CH₂Cl₂); molecular weight 468 (calc. 468.5). Epimer 22R: Melting point 150-56°C; $[\alpha]_D^{25} = +120.0^\circ$ (c=0.190; CH₂Cl₂); molecular weight 468 (calc. 468.5). The purity of the epimers was determined by HPLC-analysis to be 95.7% for the 22S-epimer (containing 1,2% of the 22R-epimer) and 98.8% for the 22R-epimer (containing 0,7% of the 22S-epimer).

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Example 6. (22R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3-20-dione.

A solution of (22R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregna-1,4-diene-3,20-dione (4.0 g) and tris(triphenylphosphine)rhodium chloride (0.40g) in 150 ml of absolute ethanol was hydrogenated at room temperature for 68 h. Water (150 ml) was added and the mixture filtered through a HV LP 0,45 μ m filter. The

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filtrate was partially evaporated. The precipitate formed was filtered leaving 1.48 g of crude product which was purified on a Sephadex LH-20 column (75 x 6.3 cm) using chloroform as mobile phase. The fraction 3600-4200 ml was collected and evaporated and further purified on a Sephadex LH-20 column (75 x 6.3 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 9825-10500 ml was collected and evaporated yielding 0.57 g of (22R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 468 (calc. 468.5). Purity: 96.5% (HPLC-analysis).

Another 220 ml of water was added to the filtrate above giving a further portion of solid product which after purification on a Sephadex LH-20 column (75 x 6.3 cm) using chloroform as mobile phase (fraction 3795-4275 ml) yielded 1.04 g of (22R)-16 α ,17 α -butylidenedioxy-6 α ,9 α -difluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 468 (calc 468.5). Purity 98.3% (HPLC-analysis).

Example 7. 6 α -Fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione.

To a suspension of 1.4 g of tris(triphenylphosphine)-rhodium chloride in 300 ml of toluene was added a solution of 1170 mg of 6 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregna-1,4-diene-3,20-dione in 250 ml of absolute ethanol. The mixture was hydrogenated 22 h at room temperature and atmospheric pressure and evaporated. The residue was precipitated from acetone-chloroform yielding 661 mg of 6 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione. Molecular weight 396 (calc. 396.5). Purity: 96.6% (HPLC-analysis).

Example 8. (22RS)-16 α ,17 α -Butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione

6 α -Fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione (308 mg) was added in portions to a solution of butanal (115 mg) and 70% perchloric acid (0.2 ml) in 50 ml

of dioxane. The reaction mixture was stirred at room temperature for 6 h. Methylene chloride (200 ml) was added and the solution washed with 10% aqueous potassium carbonate and water and dried. The residue after
5 evaporation was purified on a Sephadex LH-20 column (87 x 2.5 cm) using chloroform as mobile phase. The fraction 420-500 ml was collected and evaporated yielding 248 mg of (22R)-16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione. Melting point 85-96°C. $[\alpha]_D^{25} =$
10 +119.8° (c=0.192; CH₂Cl₂). Molecular weight 450 (calc. 450.6). Purity: 96.1% (HPLC-analysis). The distribution between the 22R- and 22S-epimers was 59/41 (HPLC-analysis).

15 Example 9. (22R)- and (22S)-Butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione
(22R)-16 α ,17 α -Butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione (225 mg) was resolved by preparative HPLC in portions on a μ Bondapak C₁₈ column (150 x 19
20 mm) using ethanol:water, 40:60, as mobile phase. The fractions centered at 265 ml (A) and 310 ml (B), respectively were collected and evaporated. After precipitation from methylene chloride - petroleum ether fraction A
yielded 68 mg of (22R)-16 α ,17 α -butylidenedioxy-6 α -fluoro-
25 -11 β ,21-dihydroxypregn-4-ene-3,20-dione. Melting point 180-192°C. $[\alpha]_D^{25} = +138.9^\circ$ (c=0.144; CH₂Cl₂). Molecular weight 450 (calc. 450.6). Purity: 99.4% (HPLC-analysis).

Fraction B gave after precipitation 62 mg of (22S)-
30 16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione. Melting point 168-175°C. $[\alpha]_D^{25} = +103.7^\circ$ (c=0.216; CH₂Cl₂). Molecular weight 450 (calc. 450.6). Purity: 99.5% (HPLC-analysis).

35 Example 10. (22R)- and (22S)-21-Acetoxy-16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β -hydroxypregn-4-ene-3,20-dione
(22R)-16 α ,17 α -Butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxy-

pregn-4-ene-3,20-dione (68 mg) was dissolved in 1 ml of pyridine. Acetic anhydride (1 ml) was added and the reaction mixture stirred at room temperature for 1 h, poured into ice-water and extracted with 3 x 25 ml of methylene chloride. The extract was dried and evaporated. The residue was chromatographed on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fractions 380-400 ml (A) and 420-440 ml (B) were collected and evaporated.

After precipitation from methylene chloride - petroleum ether fraction A yielded 14 mg of (22S)-21-acetoxy-16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β -hydroxypregn-4-ene-3,20-dione. Melting point 179-186°C. $[\alpha]_D^{25} = +86.2^\circ$ (c=0.188; CH₂Cl₂). Molecular weight 492 (calc. 492.6). Purity: 97.5% (HPLC-analysis).

Fraction B gave after precipitation 20 mg of (22R)-21-acetoxy-16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β -hydroxypregn-4-ene-3,20-dione. Melting point 169-172°C. $[\alpha]_D^{25} = +139.0^\circ$ (c=0.200; CH₂Cl₂). Molecular weight 492 (calc. 492.6). Purity: 97.9% (HPLC-analysis).

Example 11. (22R)-16 α ,17 α -Butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione.

To a solution of 20 mg of (22R)-21-acetoxy-16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β -hydroxypregn-4-ene-3,20-dione in 2 ml of ethanol, 2 ml of 2M hydrochloric acid was added. After stirring at 60°C for 5 h the reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and extracted with 3 x 25 ml of methylene chloride. The combined extracts were washed with water, dried and evaporated. The residue was purified on a Sephadex LH-20 column (87 x 2.5 cm) using chloroform as mobile phase. The fraction 460-515 ml was collected and evaporated yielding 8 mg of (22R)-16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 450 (calc. 450.6). Purity 98.4% (HPLC-

analysis).

Example 12. (22S)-16 α ,17 α -Butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione.

5 To a solution of 14 mg of (22S)-21-acetoxy-16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β -hydroxypregn-4-ene-3,20-dione in 2 ml of ethanol, 2 ml of 2M hydrochloric acid was added. The reaction, isolation and purification was performed in the same way as in Example 11. The fraction 455-510 ml was
10 collected and evaporated giving 7 mg of (22S)-16 α ,17 α -butylidenedioxy-6 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 450 (calc. 450.6). Purity: 98.6% (HPLC-analysis).

15 Example 13. 9 α -Fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione

A suspension of 3.0 g of tris(triphenylphosphine)rhodium chloride in 1000 ml of degassed toluene was hydrogenated for 45 min at room temperature and atmospheric pressure. A
20 solution of 5.0 g of triamcinolone in 500 ml of absolute ethanol was added and the hydrogenation was continued for 48 h. The reaction mixture was evaporated to dryness and suspended in 50 ml of methylene chloride. After filtration the solid phase was repeatedly washed with small portions
25 of methylene chloride and yielded after drying 4.4 g of 9 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione. Molecular weight 396 (calc. 396.5).

30 Example 14. (22RS)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β , 21-dihydroxypregn-4-ene-3,20-dione

To a solution of freshly distilled butanal (100 mg) and 0.2 ml of perchloric acid (70%) in 50 ml of purified and dried dioxane 9 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione (340 mg) was added in small portions with
35 stirring during 20 min. The reaction mixture was stirred at room temperature for another 5 h. Methylene chloride (200 ml) was added and the solution was washed with aqueous potassium carbonate and water and dried over

anhydrous magnesium sulfate. The crude product obtained after evaporation was purified on a Sephadex LH-20 column (72.5 x 6.3 cm) using chloroform as mobile phase. The fraction 2760-3195 ml was collected and evaporated yielding 215 mg of (22RS)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 450 (calc. 450.6). Purity 97.4% (HPLC-analysis).

Example 15. (22R)-and(22S)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione. (22RS)-16 α ,17 α -Butylidenedioxy-9 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione (200 mg) was resolved by chromatography on a Sephadex LH-20 column (76 x 6.3cm) using a heptane-chloroform-ethanol (20:20:1) mixture as mobile phase. The fractions 7560-8835 ml (A) and 8836-9360 ml (B) were collected and evaporated. The product from fraction A (128 mg) was identified with ¹H-NMR and mass spectrometry to be (22S)-16 α ,17 α -butylidenedioxy-9 α -fluoro-11 β ,21-dihydroxypregn-4-ene-3,20-dione and the product from the B fraction (50 mg) as the 22R-epimer.

The epimers had the following properties. Epimer 22S: Melting point 180-190°C; $[\alpha]_D^{25} = +105.6^\circ$ (c=0.214;CH₂Cl₂); molecular weight 450 (calc. 450.6). Epimer 22R: Melting point 147-151°C; $[\alpha]_D^{25} = +133.7^\circ$ (c=0.196;CH₂Cl₂); molecular weight 450 (calc. 450.6). The purity of the epimers was determined by HPLC-analysis to be 97.6% for the 22S-epimer (containing 1.8% of the 22R-epimer) and 98.2% for the 22R-epimer (containing 0.8% of the 22S-epimer).

Example 16. Pharmaceutical Preparations

The following non-limitative examples illustrate formulations intended for different topical forms of administration. The amount of active steroid in the percutaneous formulations are ordinarily 0.001-0.2% (w/w), preferably 0.01-0.1% (w/w).

	<u>Formulation 1, Ointment</u>			
	Steroid, micronized		0.025	g
	Liquid paraffin		10.0	g
	Whit soft paraffin	ad	100.0	g
5				
	<u>Formulation 2, Ointment</u>			
10	Steroid		0.025	g
	Propylene glycol		5.0	g
	Sorbitan sesquioleate		5.0	g
	Liquid paraffin		10.0	g
	White soft paraffin	ad	100.0	g
15				
	<u>Formulation 3, Oil in water cream</u>			
	Steroid		0.025	g
	Cetanol		5.0	g
	Glyceryl monostearate		5.0	g
20	Liquid paraffin		10.0	g
	Cetomacrogol 1000		2.0	g
	Citric acid		0.1	g
	Sodium citrate		0.2	g
	Propylene glycol		35.0	g
25	Water	ad	100.0	g
	<u>Formulation 4, Oil in water cream</u>			
	Steroid, micronized		0.025	g
	White soft paraffin		15.0	g
30	Liquid paraffin		5.0	g
	Cetanol		5.0	g
	Sorbimacrogol stearate		2.0	g
	Sorbitan monostearate		0.5	g
	Sorbic acid		0.2	g
35	Citric acid		0.1	g
	Sodium citrate		0.2	g
	Water	ad	100.0	g

Formulation 5, Water in oil cream

	St roid		0.025 g
	Whit soft paraffin		35.0 g
	Liquid paraffin		5.0 g
5	Sorbitan sesquioleate		5.0 g
	Sorbic acid		0.2 g
	Citric acid		0.1 g
	Sodium citrate		0.2 g
	Water	ad	100.0 g

10

Formulation 6, Lotion

	Steroid		0.25 mg
	Isopropanol		0.5 ml
	Carboxyvinylpolymer		3 mg
15	NaOH		q.s.
	Water	ad	1.0 g

Formulation 7, Suspension for injection

	Steroid, micronized		0.05-10 mg
20	Sodium carboxymethylcellulose		7 mg
	NaCl		7 mg
	Polyoxyethylene (20) sorbitan monooleate		0.5 mg
	Phenyl carbinol		8 mg
25	Water, sterile	ad	1.0 ml

Formulation 8, Aerosol for oral and nasal inhalation

	Steroid, micronized		0.1 % w/w
	Sorbitan trioleate		0.7 % w/w
30	Trichlorofluoromethane		24.8 % w/w
	Dichlorotetrafluoromethane		24.8 % w/w
	Dichlorodifluoromethane		49.6 % w/w

Formulation 9, Solution for atomization

35	Steroid		7.0 mg
	Propylene glycol		5.0 g
	Water	ad	10.0 g

Formulation 10, Powder for inhalation

A gelatin capsule is filled with a mixture of

Steroid, micronized	0.1 mg
Lactose	20 mg

5

The powder is inhaled by means of an inhalation device.

Formulation 11, Powder for inhalation

10 The spheronized powder is filled into a multidose powder inhaler. Each dose contains

Steroid, micronized	0.1 mg
---------------------	--------

Formulation 12, Powder for inhalation

15 The spheronized powder is filled into a multidose powder inhaler. Each dose contains

Steroid, micronized	0.1 mg
Lactose, micronized	1 mg

20 Formulation 13, capsule for treating the small bowel

Steroid	1.0 mg
Sugar spheres	321 mg
Aquacoat ECD 30	6.6 mg
Acetyltributyl citrate	0.5 mg
Polysorbate 80	0.1 mg
Eudragit L100-55	17.5 mg
Triethylcitrate	1.8 mg
Talc	8.8 mg
Antifoam MMS	0.01 mg

30

Formulation 14, capsule for treating the large bowel

Steroid	2.0 mg
Sugar spheres	305 mg
Aquacoat ECD 30	5.0 mg
Acetyltributyl citrate	0.4 mg
Polysorbate 80	0.14 mg

35

	Eudragit NE30 D	12.6 mg
	Eudragit S100	12.6 mg
	Talc	12.6 mg
5	<u>Formulation 15, rectal enema</u>	
	Steroid	0.02 mg
	Sodium carboxymethylcellulose	25 mg
	Disodium edetate	0.5 mg
	Methyl parahydroxybenzoate	0.8 mg
10	Propyl parahydroxybenzoate	0.2 mg
	Sodium chloride	7.0 mg
	Citric acid anhydrous	1.8 mg
	Polysorbate 80	0.01 mg
	Water, purified ad	1.0 ml

15

Pharmacology

The selectivity for local antiinflammatory activity can be exemplified by the following airway model.

A considerable fraction of inhaled GCS is deposited in the pharynx and is subsequently swallowed ending up in the gut. This fraction contributes to the unwanted side effects of the steroid since it is acting outside the area intended for treatment (the lung). Therefore, it is favourable to use a GCS with high local anti-inflammatory activity in the lung but low GCS induced effects after oral uptake. Studies were therefore done in order to determine the GCS induced effects after local application in the lung as well as after peroral administration and the differentiation between glucocorticosteroid actions in the treated lung region and outside this area were tested in the following way.

Test models

A. Test model for desired local antiinflammatory activity on airway mucosa (left lung lobe)

35

Sprague Dawley rats (250 g) were slightly anaesthetized with Ephrane and the glucocorticosteroid test preparation

(suspended in saline) in a volume of 0.5 ml/kg was instilled into just the left lung lobe. Two hours later a suspension of Sephadex (5 mg/kg in a volume of 1 ml/kg) was instilled under slight anaesthesia in the trachea well
5 above the bifurcation so that the suspension reached both the left and right lung lobes. Twenty hours later the rats were killed and the left lung lobes dissected out and weighed. Control groups got saline instead of
10 glucocorticosteroid preparation and saline instead of Sephadex suspension to determine the weight of non-drug treated Sephadex edema and the normal lung weight.

B. Test model for unwanted systemic effect by orally absorbed glucocorticosteroid

15 Sprague Dawley rats (250 g) were slightly anaesthetized with Ephrane and after that the GCS test preparation in a volume of 0,5 ml/kg was given orally. Two hours later a suspension of Sephadex (5 mg/kg in a volume of 1 ml/kg)
20 was instilled in the trachea well above the bifurcation so that the suspension reached both the left and the right lung lobes. Twenty hours later, the rats were killed and the lung lobes were weighed. Control groups got saline instead of glucocorticosteroid preparation and saline
25 instead of Sephadex suspension to determine the weight of non-drug treated Sephadex edema and the normal weight.

The results of the comparative study are given in Table 1. The pharmacological profile of the tested compound of the
30 invention was compared to that of budesonide. The results demonstrate that the compound according to example 6 shows a much higher local antiinflammatory activity than budesonide. Furthermore, the results also demonstrate a higher lung selectivity of the tested compound of the
35 invention compared to the selected prior art compound since the dose required to inhibit lung edema (ED_{50}) by oral administration of the above mentioned compound is 32 times higher and of budesonide 13 times higher than the

dose ne d d to inhibit lung dema by local application to the lung of the drugs. (Budesonide 4000 and 300 nmol/kg), exampl 6, 320 and 10 nmol/kg, r spectiv ly)

- 5 Thus it can be concluded that the compounds of the invention are well suited for local treatment of inflammatory disorders in the skin and various cavities of the body (e.g. lung, nose, bowel and joint).

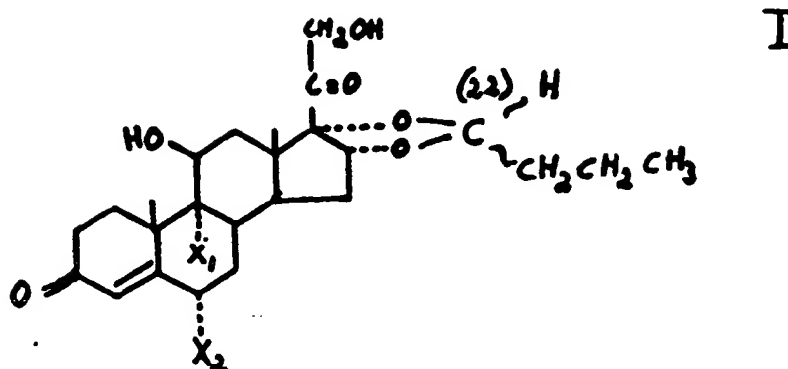
Table 1. Effects of tested glucocorticosteroids in the Sephadex induced lung edema model in the rat. The results are given in relation to the corresponding control group given Sephadex.

Compound according to examples no	Ed ₅₀ (left lung administration; nmol/kg)	Ed ₅₀ (p.o administration; nmol/kg) lung*
Budesonide	300	4000
6	10	320

* ED₅₀ = required glucocorticosteroid dose to reduce the edema by 50%.

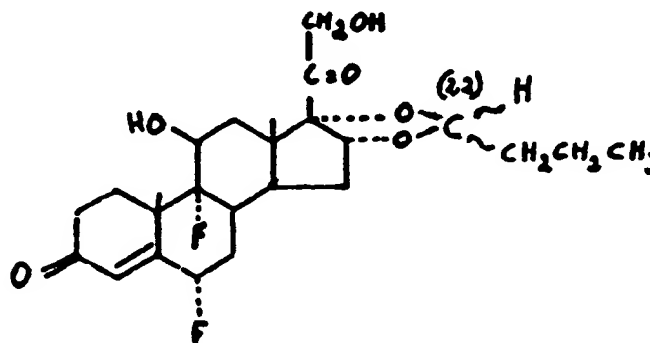
Claims

1. A 22R or 22S pimer of a compound of the general formula



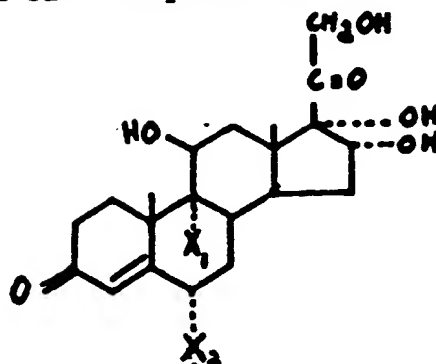
wherein X_1 and X_2 are the same or different and each represents a hydrogen atom or a fluorine atom, provided that X_1 and X_2 are not simultaneously a hydrogen atom.

2. A compound according to claim 1, characterized by being a 22R or 22S epimer of the structure

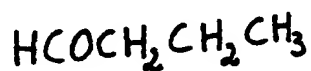


3. A compound according to any of claims 1 - 2 wherein the stereoisomeric configuration at the 22 carbon atom is R.
4. A process for the preparation of a compound of the formula I as defined in claim 1, characterized by

a) reaction of a compound of the formula

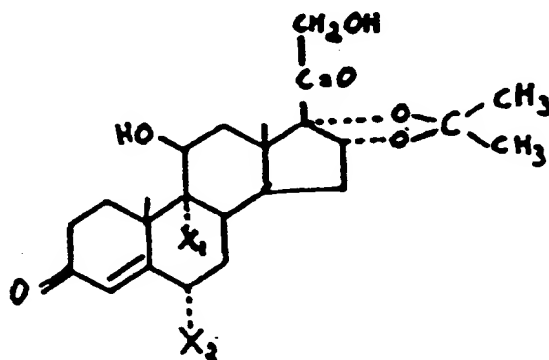


wherein X₁ and X₂ are as defined in claim 1,
with an aldehyde of the formula

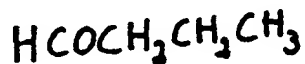


whereafter the epimeric mixture is resolved into its
stereoisomeric components, or

b) reaction of a compound of the formula



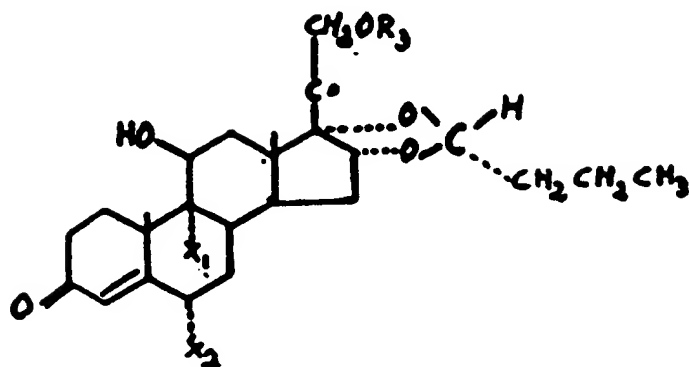
wherein X₁ and X₂ are as defined in claim 1,
with an aldehyde of the formula



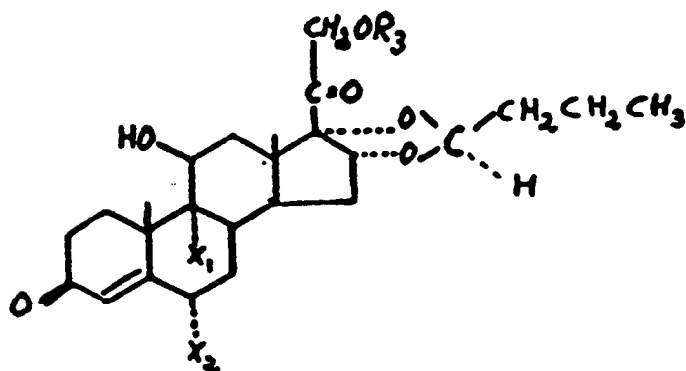
whereafter the epimeric mixture is resolved into its
stereoisomeric components,

or

c) hydrolysis of a compound of the formula



or



wherein X_1 and X_2 are as defined in claim 1 and R_3 is a carboxylic acid rest having a straight hydrocarbon chain having 1-5 carbon atoms.

5. A pharmaceutical preparation comprising as active ingredient a compound according to any of claims 1-3.
6. A pharmaceutical preparation according to claim 5 in dosage unit form.
7. A pharmaceutical preparation according to claims 5-6 comprising the active ingredient in association with a pharmaceutically acceptable carrier.

8. A compound according to any of claims 1-3 for use as a therapeutically active substance.
9. Use of a compound according to any of claims 1-3 for the preparation of medicaments with anti-inflammatory and anti-allergic activity.
10. A method for the treatment of inflammatory and allergic conditions in mammals, including man, characterized by the administration to a host in need of such treatment of an effective amount of a compound according to any of claims 1-3.
11. Compounds and processes for their preparation, pharmaceutical compositions containing them, and their use in the treatment of inflammatory and allergic conditions as claimed in claim 1 - 10 inclusive and substantially as described.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 92/00055

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 J 71/00																	
II. FIELDS SEARCHED <div style="text-align: center; border: 1px solid black; padding: 2px;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border: 1px solid black;">Classification System</th> <th style="border: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; height: 40px; vertical-align: bottom;">IPC5</td> <td style="border: 1px solid black; vertical-align: bottom;">C 07 J</td> </tr> </table> <div style="text-align: center; border: 1px solid black; padding: 2px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div> <p style="padding: 5px;">SE,DK,FI,NO classes as above</p>			Classification System	Classification Symbols	IPC5	C 07 J											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category *</th> <th style="width: 60%; padding: 5px;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 30%; padding: 5px;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="padding: 5px;">EP, A1, 0262108 (ASTRA PHARMACEUTICAL PRODUCTION AB) 30 March 1988, see the whole document --</td> <td style="text-align: center; vertical-align: top;">1-9, 11</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="padding: 5px;">EP, A1, 0054010 (AKTIEBOLAGET DRACO) 16 June 1982, see the whole document --</td> <td style="text-align: center; vertical-align: top;">1-9, 11</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="padding: 5px;">US, A, 3928326 (BRATTSAND ET AL) 23 December 1975, see the whole document --</td> <td style="text-align: center; vertical-align: top;">1-9, 11</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="padding: 5px;">ACTA PHARM. SUEC., Vol. 21, 1984 Arne Thalén et al: "Synthesis and pharmacological properties of some 16x,17x-acetals of 16x-hydroxyhydrocortisone, 16x-hydroxyprednisolone and fluorinated 16x-hydroxyprednisolones", page 109-124, see particularly page 112 --</td> <td style="text-align: center; vertical-align: top;">1-9, 11</td> </tr> </tbody> </table>			Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	EP, A1, 0262108 (ASTRA PHARMACEUTICAL PRODUCTION AB) 30 March 1988, see the whole document --	1-9, 11	X	EP, A1, 0054010 (AKTIEBOLAGET DRACO) 16 June 1982, see the whole document --	1-9, 11	X	US, A, 3928326 (BRATTSAND ET AL) 23 December 1975, see the whole document --	1-9, 11	X	ACTA PHARM. SUEC., Vol. 21, 1984 Arne Thalén et al: "Synthesis and pharmacological properties of some 16x,17x-acetals of 16x-hydroxyhydrocortisone, 16x-hydroxyprednisolone and fluorinated 16x-hydroxyprednisolones", page 109-124, see particularly page 112 --	1-9, 11
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<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search 8th May 1992 </td> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report 1992 -05- 12 </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;"> International Searching Authority <div style="text-align: center;">SWEDISH PATENT OFFICE</div> </td> <td style="border: 1px solid black; padding: 5px;"> Signature of Authorized Officer <div style="text-align: center;"> Eva Johansson </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 8th May 1992	Date of Mailing of this International Search Report 1992 -05- 12	International Searching Authority <div style="text-align: center;">SWEDISH PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center;"> Eva Johansson </div>											
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International Searching Authority <div style="text-align: center;">SWEDISH PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center;"> Eva Johansson </div>																

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	ACTA PHARM. SUEC., Vol. 24, 1987 Arne Thalén: "Epimers of budesonide and related corticosteroids", page 97-114, see particularly page 98 --	1-9, 11
A	US, A, 3929768 (BRATTSAND ET AL) 30 December 1975, see the whole document --	1-9, 11
A	EP, A2, 0164636 (SICOR SOCIETA ITALIANA CORTICOSTEROIDI S.P.A.) 18 December 1985, see the whole document -- -----	1-9, 11

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 10, because it relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv). Methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods.

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims. It is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 92/00055**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 28/03/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0262108	88-03-30	DE-A- 3774987	92-01-16
		JP-A- 63093795	88-04-25
		US-A- 4925933	90-05-15
EP-A1- 0054010	82-06-16	AU-B- 546379	85-08-29
		AU-D- 7816981	82-06-10
		CA-A- 1183835	85-03-12
		JP-C- 1451142	88-07-25
		JP-A- 57122100	82-07-29
		JP-B- 62061599	87-12-22
		SE-A- 8008524	82-06-05
		SU-A- 1156600	85-05-15
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